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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,760	11/19/2001	Shohei Koide	176/60901 (6-11402-968)	2042

7590 04/10/2007

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EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	**PAPER NUMBER**
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/006,760	KOIDE, SHOHEI	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-16,145-183 and 185* is/are pending in the application.

4a) Of the above claim(s) *145-179* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-16,180-183 and 185* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/19/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicant's amendments and remarks of 20 December 2006, in response to the 20 June 2006 Office Action, are acknowledged and have been entered.

Claim 1 has been amended. Claims 12, 109-144 and 184 have been cancelled. New claim 185 has been presented and entered.

Claims 1-11, 13-16, 145-183 and 185 are under consideration in the instant application. Claims 145-183 stand withdrawn.

Applicant requests rejoinder of claims 145-179 because each of these method claims recites the use of "a polypeptide monobody according to claim 1". Applicant's arguments have been fully considered, but have not been found persuasive. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Claim 1 has not been determined to be allowable.

Applicant traverses the withdrawal from consideration of claims 180-183. The reason for the traversal are that claims 180-183 are directed to specific species of polypeptide of claim 1. Claims 180-183, as now presented, fail to further limit claim 1, as now amended (see rejections below). In anticipation that claims will be amended to overcome rejections below, the following species elections are required.

Election of Species:

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, of **FG loop region sequences as recited in claims 180 and 182 (one SEQ ID NO:)**, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. The species are independent or distinct because each SEQ

ID NO represents an amino acid structure of unique sequence composition and structural characteristics.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, of **BC loop region sequences as recited in claim 181 (one SEQ ID NO:)**, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. The species are independent or distinct because each SEQ ID NO represents an amino acid structure of unique sequence composition and structural characteristics.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, of **AB loop region sequences as recited in claim 183 (one SEQ ID NO:)**, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. The species are independent or distinct because each SEQ ID NO represents an amino acid structure of unique sequence composition and structural characteristics.

Currently, Claim 1 is generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Information Disclosure Statement:

Applicant notes that the PTO-1449 submitted with the IDS of 18 December 2001 has not been returned. Applicant includes a date-stamped postcard as evidence that

IDS had been submitted on that date. However, the IDS appears to be lost; no IDS of that date was found among documents in the file. The IDS presented on 20 December 2006 is a resubmission of the one submitted on 18 December 2001; references cited on it are being considered.

The information disclosure statement presented on 20 December 2006 (resubmission of IDS of 18 December 2001) fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. References 2-16 have been lined through and have not been considered because the references were not submitted to the Office.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s), for references cited on IDS of 20 December 2006 will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Withdrawn Rejections

The rejection of Claims 1-16 under 35 U.S.C. 112, first paragraph for not being enabled for the full scope of the claims is withdrawn in view of applicant's amendment to Claim 1.

The rejection of Claims 1-16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicant's amendment to Claim 1.

Maintained/New Rejections

Double Patenting:

The rejection of Claims 1-11, 13-16 under the judicially created doctrine of obviousness-type double patenting is maintained for reasons of record.

Claims 1-11, 13-16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 of U.S. Patent No. 6,673,901 in view of Lipovsek et al (US 6,818,418 filed; 29 February 2000).

Applicant traverses this rejection (Remarks, 20 December 2006, page 9 paragraph 4, bridging page 10, 1st paragraph). The reason for the traversal is that claim 1 of the '901 patent, while generic does not teach or suggest the monobodies claimed in the instant invention which have nuclear receptor binding affinity. Applicant's arguments have been fully considered but are not found to be persuasive for reasons of record. Claim 1 of the '901 patent recites a fibronectin type III (Fn3) polypeptide monobody that binds to a specific binding partner (SBP) to form a polypeptide:SBP complex. The monobody is designed on the basis of a scaffold of wild-type 10th Fn3 domain of fibronectin (page 32, lines 3-5), which is identical to SEQ ID NO:2 of the instant invention. Claim 1 and the specification of the '901 patent fail to further define, or identify examples of "specific binding partner". Thus, the '901 patent does not teach any "specific binding partner". The '418 patent teaches protein variants of the tenth module of human Fn3, the protein of SEQ ID NO:2 of the instant invention. The protein taught by the '418 patent is characterized by its ability to bind to a compound that is not bound by the corresponding naturally-occurring fibronectin (column 2, lines 32-36). As an example of a binding compound, the '418 patent teaches receptor/ligand pairs (column 5, line 39). The receptor can be considered to encompass nuclear receptors.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '901 patent to obtain a fibronectin type III monobody which binds a "specific binding partner" (as taught by the 901 patent) wherein the specific binding partner is a receptor/ligand pair, encompassing a nuclear receptor, as taught by the '418 patent. The person of ordinary skill in the art would have been motivated to make these modifications and have expected success because both the '901 and the '418 patents teach polypeptides which are variants on fibronectin type III (Fn3) polypeptide which bind compounds that are not bound by naturally-occurring fibronectin.

Therefore, the monobody of the instant invention is an obvious variation of the monobody set forth in the claims of the '901 patent in view of the teachings of the '418 patent.

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13-16, 180-183 and 185 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It appears that applicant's invention comprises polypeptides which function as antibody mimics. The polypeptides are based on a scaffold of the human fibronectin domain known as the tenth human fibronectin type III domain (amino acid residues 1416-1509 of human fibronectin). The tenth human fibronectin type III domain is a sandwich of anti-parallel β-sheets, with solvent-accessible loops near the two ends of the polypeptide chain. Applicant has introduced variations in the amino acid residues of the tenth human fibronectin type III domain loops to produce polypeptides which bind nuclear receptors. However, the claims, as currently presented, fail to clearly and distinctly convey applicant's claimed invention.

Claim 1, one of the independent claims of the instant invention, is directed to a polypeptide "monobody". "Monobody" is a term defined by applicant and his coworkers as variants of the tenth human fibronectin type III domain with novel binding functions, (page 2, lines 18-20 and Koide et al. 1998. J Mol Biol 284:1141-1151, page 1142, 1st column, 3rd paragraph). Claim 1 is vague and indefinite in not specifically defining the structure of the monobody required to accomplish the recited function of nuclear receptor binding activity. The claim recites a "loop region sequence linked between adjacent β-strand domain sequences". It is unclear what these loop and β-strand domains encompass. The claim recites "optionally, an N-terminal tail of at least about 2

amino acids, a C-terminal tail of at least about 2 amino acids, or both." It is unclear if applicant intends the full length fibronectin molecule to meet the limitations of the claim, since the claim does not recite an upper limit to the number of amino acids at the N- or C- termini. Furthermore, the claim recites "wherein at least one loop region sequence.....comprises an amino acid sequence which varies by deletion, insertion or replacement of at least two amino acids from a corresponding loop region.....". It is unclear if applicant intends to delete or replace an entire loop region of the monobody, or insert an additional loop sequence, since no upper limit to the number of amino acids to be deleted, inserted or replaced is recited.

Claim 9 is vague and indefinite in reciting "wherein said at least two Fn3 β-strand domain sequences A through G....". It is unclear what portion of the Fn3 sequence is encompassed by domains labeled A through G. Additionally, it is unclear what applicants intend by "derivatives thereof". It is unclear if applicants intend derivatives of a tenth Fn3 domain human fibronectin, derivatives of β-strand domain sequences or something else entirely. Additionally, the claim is vague and indefinite in reciting "wherein the loop region sequences comprise an AB loop, a BC loop, a CD loop, a DE loop, an EF loop and an FG loop". It is unclear what portion of the Fn3 sequence is encompassed by the term "loop region sequences". Thus, the metes and bounds of the claim cannot be determined.

Claim 10 is vague and indefinite in reciting "wherein the at least one loop region sequence is selected from the group consisting of the AB loop region sequence, the BC loop region sequence, the DE loop region sequence, and the FG loop region sequence and combinations thereof". It is unclear what portion of the Fn3 sequence is encompassed by the term "loop region sequences". Furthermore, it is unclear what applicant intends by combinations thereof; one cannot determine how many loops are to be in the combinations. It is unclear if a combination is to be one (large) loop comprising the sequences of several recited loop sequences, or a monobody comprising one or more loop region sequences linked between adjacent β-strand domain sequences.

Claim 11 is vague and indefinite in reciting "wherein the at least one loop region sequence is a combination of the BC loop region sequence and the FG loop region sequence". It is unclear what portion of the Fn3 sequence is encompassed by the term "loop region sequences". Furthermore, it is unclear if a combination is to be one (large) loop comprising the sequences the BC loop region and the FG loop region fused to each other, or a monobody comprising the BC loop region and the FG loop region linked between adjacent β-strand domain sequences.

There is no antecedent basis in claim 1 for the recitation of "FG loop region sequence" in claims 180 and 182.

There is no antecedent basis in claim 1 for the recitation of "BC loop region sequence" in claim 181.

There is no antecedent basis in claim 1 for a recitation of "AB loop region sequence" in claim 183.

Claim 185 is vague and indefinite in reciting "β-strand domain sequences A through G....". It is unclear what amino acid residues would be encompassed by β-strand domain sequences A through G. Furthermore, the claim recites "and loop region sequences AB, BC DE, EF, and FG". It is unclear what portion of the Fn3 sequence is encompassed by the term "loop region sequences". Additionally, the claim recites wherein at least one loop region sequence selected from the group of AB, BC, FG and combinations thereof, varies by deletion, insertion or replacement of at least two amino acids from .....". It is unclear how many loop sequences or to included in a combination; it is unclear if the recited combination is to be the several recited loop sequences fused together to form one large loop sequence, or a monobody comprising the AB, BC and FG loop region linked by adjacent β-strand domain sequences. It is unclear if applicant intends to delete or replace an entire loop region of the monobody, or insert an additional loop sequence, since no upper limit to the number of amino acids to be deleted, inserted or replaced is recited.

Claims 2-8, and 13-16 are included in this rejection as depending from rejected claims.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-11, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Pasqualini et al. (13 July 1999. US 5,922,676, the '676 patent). Claim 1 recites a fibronectin type III polypeptide comprising a polypeptide wherein ....the N-terminal tail.....comprises an amino acid sequence which varies by deletion....of at least two amino acids from a ....N-terminal tail in a tenth Fn3 domain of fibronectin having the amino acid sequence of SEQ ID NO:2. The '676 patent teaches an amino acid sequence, SEQ ID NO:8 that is 98% identical to SEQ ID NO:2 of the instant invention (100% local similarity). SEQ ID NO:8 differs from SEQ ID NO:2 of the instant invention by deletion of two amino acids at the N-terminal tail, thereby meeting the limitations of Claim 1. The III-10 polypeptide is described as a fragment of fibronectin, corresponding to residues 1416-1509 in fibronectin (Column 7, lines 39-42). The patent teaches protein expressed as fusion protein with the bacterial glutathione-S-transferase (GST) protein (Column 15, lines 12-14). The '676 patent does not teach a polypeptide that exhibits nuclear receptor binding wherein the nuclear receptor is a steroid receptor, or an estrogen receptor or wherein the polypeptide exhibits estrogen receptor binding activity in the presence of an estrogen receptor agonist or antagonist; however, the polypeptide of SEQ ID NO:8 meets the limitation of Claim 1 as recited. Case law has established that the discovery of a previously unappreciated property of a prior art

composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Also, case law has established that a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Therefore, absent evidence to the contrary, the prior art discloses exactly what is claimed in Claims 1-11, 13 and 14 of the instant application.

Claims 1-11, 13-15, and 185 are rejected under 35 U.S.C. 102(b) as being anticipated by Koide (1998. WO 98/56915, cited on IDS). Koide teaches a fibronectin type III (Fn3) polypeptide monobody. The monobody is designed on the basis of a scaffold of wild-type 10^{th} Fn3 domain of fibronectin (page 32, lines 3-5), which is identical to SEQ ID NO:2 of the instant invention. The WO document teaches a polypeptide monobody comprising a plurality of Fn3 β-strand domain sequences that are linked to a plurality of loop region sequences. One or more of the monobody loop region sequences of the Fn3 polypeptide vary by deletion, insertion or replacement of at least two amino acids from the corresponding loop region sequences in wild-type Fn3. The β-strand domains of the monobody have at least about 50% total amino acid sequence homology to the corresponding wild type sequence. One or more of the loop regions of the monobody comprise amino acid residues of the AB loop, the BC loop, the CD loop, the DE loop, the EF loop and the FG loop (page 6, lines 12-26). The WO document teaches fusion proteins comprising His-tags (page 21, line 4). The monobody is disclosed as capable of binding to a specific binding partner (abstract and page 8, lines 8-10). The specific binding partner is not further identified or characterized. The WO document does not teach a polypeptide that exhibits nuclear receptor binding wherein the nuclear receptor is a steroid receptor, or an estrogen receptor or wherein the polypeptide exhibits estrogen receptor binding activity in the presence of an estrogen receptor agonist or antagonist; however, the polypeptide disclosed by Koide meets the limitation of Claim 1 as recited. The specific binding partner taught by Kiode would encompass a nuclear receptor. Case law has

established that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Also, case law has established that a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Therefore, absent evidence to the contrary, the prior art discloses exactly what is claimed in Claims 1-11, 13-15 and 185 of the instant application.

Claims 1-11, 13, 14, and 185 are rejected under 35 U.S.C. 102(e) as being anticipated by Lipovsek et al. (16 November 2004. US 6,818,418, filed 29 Feb. 2000, the '418 patent). The '418 patent teaches proteins which are variants of the tenth module of human Fn3, the protein of SEQ ID NO:2 of the instant invention (column 8, lines 6-9). The protein has at least one randomized (variant) loop (abstract). The protein taught by the '418 patent is characterized by its ability to bind to a compound that is not bound by the corresponding naturally-occurring fibronectin (column 2, lines 32-36). The fibronectin type III domain-containing proteins may be formulated as part of a fusion protein (column 2, lines 53-54). The "fibronectin type III domain" is a domain having 7 or 8 beta strands which are distributed between two beta sheets, and further containing loops which connect the beta strands to each other and are solvent exposed. There are at least three such loops at each edge of the beta sheet sandwich (column 4, lines 37-46). As an example of a binding compound, the '418 patent teaches receptor/ligand pairs (column 5, line 39). The receptor can be considered to encompass nuclear receptors. The '418 patent does not teach a polypeptide that exhibits nuclear receptor binding wherein the nuclear receptor is a steroid receptor, or an estrogen receptor or wherein the polypeptide exhibits estrogen receptor binding activity in the presence of an estrogen receptor agonist or antagonist; however, the polypeptide disclosed by the '418 patent meets the limitation of Claim 1 as recited. Case law has established that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does

not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Also, case law has established that a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Therefore, absent evidence to the contrary, the prior art discloses exactly what is claimed in Claims 1-11, 13, 14 and 185 of the instant application.

Conclusions:

No claims are allowed. In view of new grounds of rejection, this action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS

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